Failure of Short-Course Ceftriaxone Chemotherapy for Multidrug-Resistant Typhoid Fever in Children: a Randomized Controlled Trial in Pakistan

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The precise duration of therapy of multidrug-resistant (MDR) typhoid with broad-spectrum cephalosporins is uncertain. We prospectively randomized 57 children with culture-proven MDR typhoid to receive treatment with intravenous ceftriaxone (CRO) (65 mg/kg of body weight/day) for 7 days (short course; $n = 29$) or 14 days (conventional; $n = 28$). The response to therapy, as evaluated by the serial monitoring of the typhoid morbidity score and bacteriological clearance, was comparable between groups. In contrast to the conventional therapy, 14% of the children receiving CRO for 7 days had a confirmed bacteriological relapse within 4 weeks of stopping therapy.

Typhoid fever is widely prevalent in developing countries, with an annual burden of 16 million cases globally (16). The emergence of drug-resistant strains in recent years, especially multidrug-resistant (MDR) *Salmonella typhi* (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), has been of major concern (21). Given the considerable morbidity associated with MDR typhoid in children (5) and increased mortality with delay in treatment (6), it is imperative that appropriate antibiotic therapy be instituted promptly. Oral quinolones have provided an effective oral form of therapy for MDR typhoid in adults but are still not licensed for widespread pediatric use. Where the generic use of quinolones has become widespread, there are also recent disturbing reports of emerging quinolone resistance (9, 25). Broad-spectrum cephalosporins have thus remained an important therapeutic alternative for the therapy of MDR typhoid in children, with excellent primary cure rates (11, 12, 19). We have previously described successful cures of MDR typhoid in hospitalized children receiving therapy with intravenous (i.v.) ceftriaxone (CRO) for 14 days (3, 7); the children were evaluated in accordance with recommendations for the evaluation of anti-infective agents for treating typhoid (10). However, the cost of therapy with a 14-day course of CRO is considerable, frequently beyond the capacity of health care budgets (7). Several studies have therefore explored the potential of shorter courses of CRO for treating typhoid, ranging from 3 to 7 days, with impressive cure rates (1, 11, 14, 17, 22), but only a few such studies (1, 11, 22) have involved patients, especially children, with MDR typhoid.

In order to evaluate a shorter course of therapy with CRO, we designed a prospective randomized controlled trial of either 7 or 14 days of CRO treatment for children admitted with culture-proven MDR typhoid, with an objective evaluation of clinical and microbiological responses to therapy. The sample size of the study (28 patients per treatment group) was determined based on the assumption of a 50% reduction in the cost of therapy for a 7-day course; the cost of therapy for a 14-day course of CRO is Rs.6400 (US$280) (20). Comparative data on baseline characteristics and respective outcomes were evaluated by analysis of variance or chi-square test (with the Yates correction), as required.

For all patients with suspected typhoid, a complete blood count, blood culture, malarial film, and Widal test and liver function test results were obtained. For those who had received previous antibiotic therapy for ≥72 h, a bone marrow culture was also obtained. Five milliliters of blood or bone marrow was inoculated into two blood culture bottles, each containing either brain heart infusion broth or thioglycolate broth. The cultures were examined thereafter for growth at different stages and then subcultured, and positive colonies were identified biochemically with API 20E strips (Analytab Products, Plainview, N.Y.). The sensitivity to respective antibiotics was determined by the Kirby-Bauer disk diffusion method (2).

The protocol of this study was approved by the Human Subjects Protection Committee at The Aga Khan University Medical Center (AKUMC). All children with suspected typhoid fever presenting to the ambulatory care services at AKUMC who were ill enough to require hospitalization were potentially eligible for the study. After giving informed written consent, children with proven MDR typhoid were allocated to either 7- or 14-day therapy with once daily i.v. CRO (65 mg/kg of body weight/day) by a block randomization method that used sealed envelopes. A previously validated composite score of clinical features, i.e., the typhoid morbidity score (TMS), was used to objectively assess response to therapy (3, 4) (Table 1). This score was evaluated for all patients at admission and daily thereafter until completion of the protocol. In all cases, repeat blood cultures were obtained at days 3 and 7 or thereafter as clinically indicated. A blood sample was also obtained among those considered a "clinical failure" of therapy, which was defined as the persistence of fever along with a <2-point reduction in TMS by day 7 of therapy, whereas the persistence of *S. typhi* in cultures obtained at day 3 or thereafter was considered a "bacteriological treatment failure." Relapse was defined as the recurrence of fever along with a positive blood culture for *S. typhi* with a similar antibiogram to the original infecting strain within 8 weeks of the completion of therapy. Given the low yield of urine cultures at follow-up (8) and our previous experience of poor sensitivity among stool cultures

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TABLE 1. Characteristics for determining typhoid morbidity score[a]

Characteristic	Degree of condition resulting in score of:		
	0	1	2
Fever	≤37.5°C	37.6–39.0°C	>39.0°C
Mental state	Clear	Irritability	Delirium; coma
Liver size	Not palpable	≤2.5 cm	>2.5 cm
Diarrhea	None	Mild	Severe
Vomiting	None	Nausea	Vomiting
Abdominal pain	None	Diffuse pain	Right hypochondrial tenderness
Result of abdominal examination	Normal	Abdominal distension; doughy feel	Ileus; peritonitis; gastrointestinal bleeding

[a] Based on a previously validated scoring system (3).

from children with typhoid in Karachi (5), no attempt was made to screen the urine or stool cultures of the patients after discharge.

Of 118 consecutive children with suspected typhoid who were admitted to AKUMC, an alternative diagnosis was established within 48 h of admission for 87 of them. For an additional 19 patients, the *S. typhi* specimen isolated from them was sensitive to first-line antibiotics, and they were thus placed on appropriate antibiotics. For five additional children, although the cultures were negative, there was supportive serological evidence of typhoid on a Widal test. The patients with presumed typhoid fever were placed on oral amoxicillin for 14 days, and all recovered. In all, 57 children had MDR *S. typhi* specimens isolated from blood and/or bone marrow cultures and were randomized to either 7- or 14-day therapy with i.v. CRO. All isolates of MDR *S. typhi* were fully resistant to disk diffusion testing to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole and were fully sensitive to CRO. Table 2 details the admission, clinical, and laboratory characteristics of the two study groups, as well as the respective outcomes. The responses to therapy for both treatment groups were comparable, and although three children were still febrile by the end of the stipulated course of therapy, there were no primary bacteriological treatment failures. In all cases of relapse, a *S. typhi* specimen with a similar antibiogram to the original isolate was identified from blood cultures. All patients who relapsed were treated with i.v. aztreonam and recovered uneventfully.

Our data suggest that despite comparable bacteriological and clinical cure rates, a 7-day course of therapy with CRO was associated with a significantly higher rate of relapse in children hospitalized with MDR typhoid, in comparison with a 14-day course of treatment. These data are at variance with information from other studies of short-course therapy with CRO for adults and children with typhoid. However, despite adequate documentation of a cure, few of the latter studies had an adequate follow-up period and did not address the issue of relapse. In addition, most studies of short-course therapy with CRO have been for infections caused by sensitive strains of *S. typhi*. In Vietnam, where there was an overall 63% incidence of MDR typhoid, Smith et al. observed a 28% primary treatment failure for a 3-day course of CRO therapy (22). In contrast, a 95% cure rate was seen among children with MDR typhoid in Egypt who were randomly selected to receive a 5-day course of CRO (11). In the latter study, Girgis et al. (11) also observed that the time-to-defervescence with CRO was only 3.9 days, which was considerably shorter than the observed pattern of defervescence for MDR typhoid in other parts of Asia (1, 7, 14, 15). It is thus possible that these differences in response to therapy may represent differences in the virulence and antibiotic responsiveness of different strains of *S. typhi*. Recent data

from Asia also underscore the considerable genetic diversity among isolates of *S. typhi* (23). It is therefore imperative that therapeutic strategies for treating MDR typhoid in children must take local epidemiological patterns and strain specificities into account.

Members of our group (4, 6) and others (18) have previously highlighted the higher toxicity and morbidity of MDR typhoid among children in south Asia. Our data provide additional evidence that a 7-day course of therapy with CRO was associated with a significantly higher and unacceptable relapse rate in Pakistani children with MDR typhoid, in comparison with concurrent controls. This relapse rate was also significantly higher than that observed previously among children from the same center with MDR typhoid who were treated with CRO for 14 days (3, 7, 19). The reasons for the observed high relapse rate after 7 days of therapy with CRO are uncertain. Although the clinical response and bacteriological clearance rates during

TABLE 2. Comparative clinical and laboratory characteristics of therapy groups

Characteristic	Value for group[a]	
	Short-course therapy	Conventional therapy
Patient data		
No. of subjects	29	28
Age (years)	7.1 ± 3.7	5.6 ± 3.4
Gender (male:female)	16:13	16:12
Weight (kg)	18.9 ± 8.7	17.2 ± 8.5
Height (cm)	113.3 ± 30.4	108.4 ± 22.6
Mid-arm circumference (cm)	19.7 ± 2.4	14.6 ± 2.4
Duration of illness (days)	11.7 ± 7.4	15.1 ± 14.8
Baseline investigations		
Hemoglobin (g/dl)	10.8 ± 1.6	10.7 ± 1.7
White blood cell count (10^9/liter)	9.1 ± 4.6	9.6 ± 4.2
C-reactive protein (mg/liter)	82.3 ± 73.4	71.5 ± 47.1
Alanine aminotransferase (IU/liter)	42.9 ± 32.9	90.6 ± 157.9
Alkaline phosphatase (IU/liter)	157.4 ± 140.9	177.1 ± 128.4
Outcome		
TMS (admission)	4.1 ± 2.4	4.4 ± 2.2
TMS (day 3)	2.4 ± 2.0	3.0 ± 2.3
TMS (day 7)	0.6 ± 1.6	0.9 ± 1.6
Time to defervescence (days)	5.4 ± 3.2	5.2 ± 3.2
Time to return of appetite (days)	4.7 ± 3.1	4.6 ± 3.0
Clinical failure	2 (7%)	1 (4%)
Bacteriological failure	—	—
Relapse	4 (14%)[b]	—

[a] Data are means ± standard deviations, where applicable.
[b] $\chi^2 = 4.2$, $P < 0.05$. All other differences are nonsignificant.

the period of hospitalization were comparable for both groups, it is possible that a 7-day course was inadequate in clearing *S. typhi* from the macrophages within the reticuloendothelial system, thereby provoking a relapse. It is also possible that in contrast with sensitive strains of *S. typhi*, MDR isolates are more virulent, with comparatively greater involvement of the reticuloendothelial system. This is supported by recent data from Vietnam, which describes increased quantitative bacteremia in cases of MDR typhoid and is suggestive of increased virulence of infective MDR strains of *S. typhi* (24). Some support for this contention can be also seen from a previous study of MDR typhoid in Karachi (4) correlating high circulating levels of interleukin-6 at admission with correspondingly higher relapse rates. We would therefore urge considerable caution in treating MDR typhoid with i.v. CRO for ≤7 days. It is uncertain if an intermediate course of therapy, one between 7 and 14 days, would be adequate for treating MDR typhoid, and further studies are needed to explore this issue.

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